Chapter 8

Metabolism

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Human space travelers are affected by a wide range of factors associated with spaceflight, the space environment, and the artificial nature of the living environment. The most significant of these factors probably is weightlessness. Living things that evolved on Earth have never been exposed to weightlessness; thus, adaptation to this unique factor must be achieved through the same physiological mechanisms that regulate adaptive responses and metabolic processes on Earth.

Homeostasis in the space environment is maintained through neurohumoral regulation of metabolism, fluid and electrolyte homeostasis, and major physiological systems, such as the cardiovascular, gastrointestinal, musculoskeletal, and blood systems. The metabolic effects of exposure to weightlessness result from the interaction of afferent inputs from different sensory systems, shifts in the circulatory system, and physical unloading of the musculoskeletal apparatus. Psychological stress and reductions in motor activity also confer additional stresses. Metabolic adaptation is accomplished through mobilizing body energy resources and supplying the necessary biochemical materials to support the functions and defense mechanisms that maintain or restore internal homeostasis. Homeostatic mechanisms are regulated through interaction of neurohumoral and endocrine systems, aspects of which can have broad "normal" ranges. The inherent flexibility in catabolic and anabolic metabolic systems ensures that vital parameters such as osmotic pressure, oxygen tension, and fluid and electrolyte levels can be kept stable under a wide range of external conditions.

Studies of human metabolism during early space exploration have revealed both sporadic and regular changes that were affected by flight duration, the time at which postflight measures were collected, and individual differences among crew members. These changes included cumulative psychological stress,[1,2] shifts in blood-cholesterol concentrations during flight, changes in blood enzyme activity and amounts and excretion of hormones, variability of metabolic indicators of adrenergic activity, and decreases in red blood cell mass and plasma volume.[1,3–5]

Fluid and electrolyte metabolism also fluctuated during flight, taking the form of dehydration and eventual loss of body mass (3 to 8% of baseline).[1,3,6] Body mass was usually regained 2 or 3 days after landing. Dehydration was accompanied by high concentrations of electrolytes in urine. Postflight examinations revealed slight changes in blood concentrations of electrolytes and osmotically active substances that were related to mission duration.

Studies of mineral metabolism in Gemini-7 crew members during flight showed negative calcium, potassium, phosphorus, and sulfur balances.[2] Analogous results were reported for Soyuz-9 cosmonauts.[1] Changes in protein metabolism have long been suspected by virtue of the slow rate at which weight is regained after long flights. Total nitrogen excretion during the 18-day Soyuz-9 mission was near the upper limit of normal; crew members on the 14-day Gemini-7 mission were in negative nitrogen balance. Although the level of tissue catabolism during these flights was not dangerous, it continues to pose concern with regard to crew health during long missions. The series of detailed, well-designed metabolic studies conducted on the U.S. Skylab missions in the 1970s are described in Chapter 4 of this volume.

Ongoing developments in space technology have allowed mission durations and complexities to be increased substantially. Long missions on the Salyut and Mir stations have included studies of the human biochemical response to spaceflight. The goal of these investigations has been to monitor the condition of cosmonauts comprehensively in order to elucidate the effects of spaceflight factors—especially weightlessness—on humans. Most biochemical data have been collected before and after flight; in-flight measurements are relatively rare. Thus, most biochemical results reflect postflight responses of individuals who have adapted to the weightless environment.

This chapter presents findings on human metabolism from studies conducted in space and in simulation experiments. Topics include protein, carbohydrate, lipid, and vitamin metabolism; blood enzyme activity; and red blood cell metabolism.

I. Protein (Nitrogen) Metabolism

All metabolic processes involve structural proteins, enzymes, and other functionally active proteins. Each amino acid in a protein has its own "metabolic life" and contributes to events such as gluconeogenesis, lipogenesis, energy production, and the formation of biologically active nitrogen compounds.

Most body nitrogen comes from ingested protein. Body nitrogen level is a function of total protein intake and assimilation, mix of amino acids, and total food calories. Current space diets contain sufficient total protein and mixtures of amino acids appropriate for human survival under spaceflight conditions, and the number of calories provided is sufficient to support normal protein metabolism. Protein assimilation (anabolism) has yet to be studied directly during flight, but has been noted to decrease during prolonged bed rest, during which subjects consumed dehydrated food. Thus, protein metabolism during spaceflight may be affected by factors other than diet (for example, decreased appetite).

Skeletal muscle constitutes about half of the human body mass and contains most of the protein. Weightlessness, in combination with limited motor activity, markedly affects skeletal muscle. Thus, changes in protein metabolism in flight are likely to be associated with diminished motor activity and altered muscle biochemistry. Both spaceflights and simulations thereof with humans and animals have revealed decreases in muscle mass, primarily in those muscle groups that are most active in normal gravity (i.e., the lower extremities), and changes in body composition involving increased body fat and diminished muscle mass.[3,7,8]

Negative nitrogen balance was observed on the Gemini-7 mission. Urinary nitrogen excretion was increased in Soyuz, Apollo, Skylab, Salyut, and Mir crew members. The amount of urea, the end-product of protein metabolism, in blood increased only slightly in cosmonauts 1 or 7 days after missions of different durations (Table 1) and in subjects after prolonged bed rest.[1,9,10] However, most postflight studies (Table 1) and simulations have revealed elevations in urinary urea and uric acid concentations.[2,3,5,9]

Altered nitrogen metabolism in flight is accompanied by the presence of amino acids in the urine. Most of the amine nitrogen found in urine is from amino acids or peptides with free amino groups. Elevated renal excretion of amine nitrogen has been observed repeatedly after spaceflight and its simulations. Aminoaciduria in bed rest consisted mostly of glycine, alanine, and tyrosine, all of which were excreted at much higher levels than before bed rest; amounts of valine, phenylalanine, leucine, isoleucine, and cysteine in urine, by contrast, were reduced after bed rest.[11]

Increased excretion of the products of protein metabolism is caused by the predominance of catabolic over anabolic processes, especially in skeletal muscles, because of muscular unloading and relative disuse in weightlessness and limited mobility. This conclusion is supported by reports of creatine and creatinine excretion in flight. Dystrophic processes in muscle promote creatinine formation, both from phosphocreatine and from dehydrated creatine. When creatinine assimilation by muscles is impaired, the resulting excess is excreted in urine. The same process occurs when some muscle fibers atrophy.

Creatinuria is common in humans undergoing bed rest; interestingly, we found creatinuria to increase when subjects confined to bed performed physical exercise. We track creatinuria in bed rest using the creatinine ratio (i.e., mg of creatinine in urine per kg of body mass) and the creatinine/nitrogen ratio (percent of creatinine in total urinary nitrogen).

Free amino acids in blood can be used to track the rates of tissue anabolism and catabolism. Plasma amino acids tend to be decreased after spaceflight relative to before, with larger decreases found after longer flights.[12,13] Decreased amounts of blood methionine, phenylalanine, cysteine, tyrosine, glycine, glutaminic acid, and serine were found after an 18-day mission; most amino acids, especially cysteine and asparagine, were depressed after a 49-day mission; all were depressed after a 140-day mission, especially histidine, methionine, and cysteine. Interestingly, blood amino acids were elevated after 120 days of bed rest with head-down tilt; hyperalaninemia was of particular interest because of the role of alanine in hepatic transamination and gluconeogenesis.[14,15]

Proteins in blood also reflect protein metabolism in tissues and the body as a whole. Total plasma protein and its fractional components have been assessed on many long space missions (Table 1). Total blood-plasma protein and albumin were increased on the day of landing in the Skylab crews; decreases in these measures on the third and 14th days after landing were accompanied by elevations in plasma volume.[4] Decreases in total protein and increases in the percentages of α-1 and α-2-globulin were noted after long Mir missions. Reductions in γ-globulin to less than preflight measures were consistent with reports of reduced immune resistance in flight and simulations (see Chapter 6, this volume). Levels of α-globulin tended to decrease, and γ-globulin increase, after a 12-month mission.[16]

Changes in blood-protein constituents were studied periodically during a 370-day period of bed rest with head-down tilt ($-5°$).[17] Blood protein increased at the end of the second month, declined, and then rose again toward the end of the bed-rest period. During the recovery period, protein content diminished, but did not return to baseline until day 30 of recovery. Changes in total globulins resembled those in protein. Albumin levels rose during the second half of the experiment. A decline in the ratio of albumin to globulin was observed only once, on the 50th day of bed rest. During the final bed-rest phase, α-2 globulin levels began to recover, probably because of the countermeasures used during that time. The rise in β-globulins probably was related to an increase in low-density, atherogenic lipoproteins that are typical of limited physical activity. A transient increase in α-globulins (relative to the final bed-rest period) was noted early in the recovery period.[18]

Attenuated flow of energy through the body could be another reason why protein synthesis is reduced in weightlessness or its simulations. Experimental results indicate that disruption of energy metabolism is less extreme in the myocardium than in skeletal muscles, but protein synthesis in the former is increasingly inhibited with duration of exposure to space or its simulations. Protein synthesis also requires a certain amount of potassium, which is excreted during spaceflight to a greater extent than on Earth; however, high-potassium diets do not intensify protein synthesis.

Table 1 Blood concentrations of protein-nitrogen metabolites in Mir crew members before (L–30) and after (R+1, R+7) flights

Flight duration, days	Subjects	Urea, mmole/L [normal 2.8–8.9]			Uric acid, μ/L [normal 119–459]			Creatinine, μ/L [normal 80–141]			Protein, g/L [normal 60–84]			Albumin, % [normal 53–63%]		
		L–30	R+1	R+7	L–30	R+1	R+7	L–30	R+1	R+7	L–30	R+1	R+7	L–30	R+1	R+7
125	K-1	7.9	8.6	7.3	—	—	—	—	—	—	81	84	72	64.5	62.0	64.5
	K-2	4.2	4.7	4.6	—	—	—	—	—	—	84	80	73	69.8	70.6	67.0
131	K-1	4.7	12.1	6.3	307	283	252	106	120	89	82	88	70	62.8	65.6	64.2
	K-2	5.3	10.5	3.1	395	387	335	109	116	82						
151	K-1	5.7	5.3	4.8	691	283	283	126	106	98	72	72	66	60.3	64.8	—
	K-2	4.9	7.7	5.0	436	204	225	68	126	93	70	82	65	67.5	63.2	—
160	K-2	7.5	7.2	7.7	582	390	430	101	92	68	79	82	61	64.2	62.4	62.2
166	K-1	8.3	7.7	6.0	402	230	364	82	106	82	71	70	74	63.2	62.1	63.0
	K-2	7.0	5.7	6.0	353	164	319	85	107	90	72	66	76	62.2	64.9	62.1
175	K-3	—	7.3	5.1	—	410	427	136	142	107	80	77	81	59.8	61.7	61.5
179	K-1	5.6	6.5	3.8	313	252	360	132	115	106	79	73	72	60.8	63.2	66.1
	K-2	5.8	6.0	3.8	202	128	220	123	96	85	74	75	69	61.0	63.6	65.3
241	K-3	3.4	9.0	6.7	286	248	248	116	127	98	70	72	58	52.0	62.6	—
326	K-1	—	7.9	5.3	—	390	350	117	65	113	73	50	85	63.7	63.5	60.9
366	K-1	4.9	3.5	3.4	305	407	219	88	105	98	78	80	72	59.0	62.6	63.3
	K-2	5.7	6.4	5.8	365	458	464	95	99	153	73	68	67	62.3	66.2	65.0

Protein catabolism also could be related to stress responses during the acute phase of adaptation to weightlessness. Stress responses such as adrenal-gland stimulation are characterized by inhibition of anabolic processes and activation of catabolic ones, particularly in skeletal muscles. High levels of ACTH and glucocorticoids antagonize the anabolic effects of insulin, and activate tissue proteolytic enzymes, peptidases, and aminotransferases, all of which increase proteolysis.

In summary, then, weightlessness seems to cause systemic changes that are manifested by shifts in nitrogen metabolism. Decreased functional loading in weightlessness leads to less-intense protein metabolism, as indicated by the prevalence of catabolic processes over anabolic ones in muscle protein; insufficient assimilation of amino acids; diminished energy consumption by muscle tissue (decreased creatinine clearance); decreased metabolism of nucleic acids (elevated uric acid excretion); and changes in blood protein and protein fractions. Changes in anabolic and catabolic metabolism indirectly affect immune resistance and γ-globulin production. However, these results should be interpreted cautiously, as the effects of countermeasures, especially exercise, no doubt confound them.[19]

II. Carbohydrate Metabolism

The total amount of carbohydrate in the body is much less than that of protein and fat. However, being the primary energy source, carbohydrates are critical to life. The chief index of carbohydrate metabolism is blood sugar. Moderate hyperglycemia and increased amounts of insulin have been reported after most space missions[2] (Table 2); however, in-flight blood glucose levels in Skylab crew members were slightly less than preflight measurements.[4]

Hypoglycemia in weightlessness and simulations thereof could be caused by increased utilization of sugars; this possibility is supported by reports of increased amounts of blood lactate and pyruvate, both oxidized products of glucolysis (Table 2). In-flight hypoglycemia also could be caused by concurrent decreases in insulin (Fig. 1). This assumption is based on biochemical data obtained from the Skylab missions,[4] postflight examinations of crew members, rat experiments on Kosmos biosatellites, and ground simulations. This assumption is also supported by results of glucose-tolerance tests in crew members at various times during flight and in bed-rest subjects (further details are given in Chapter 9 of this volume).

Although investigations of carbohydrate metabolism in flight are limited, extensive ground-based experiments on animals and humans have aided the understanding of this process. Gastrointestinal digestion of carbohydrates in animals and humans exposed to hypokinesia proceeds without appreciable deviation. Cyclic changes in the activities of amylase and invertase have been noted, as has a tendency toward at-

Table 2 Blood concentrations of carbohydrate and lipid metabolites in Mir crew members before (L–30) and after (R+1, R+7) flights

Flight duration, days	Subjects	Glucose, mmole/L [normal 3.9–5.5]			Lactate, mmole/L [normal 0.7–2.2]			Pyruvate, μ/L [normal 0–134]			Triglycerides, mmole/L [normal 0.15–2.28]			Unesterified fatty acids, ug equiv/L [normal 90–600]		
		L–30	R+1	R+7	L–30	R+1	R+7	L–30	R+1	R+7	L–30	R+1	R+7	L–30	R+1	R+7
125	K-1	—	4.8	—	1.0	2.5	2.2	43	119	94	1.4	2.1	2.1	273	286	106
	K-2	3.5	4.9	4.6	0.9	1.0	1.7	69	93	68	1.0	1.0	1.0	239	176	223
131	K-1	4.7	5.7	4.8	1.8	2.3	1.2	122	23	76	0.9	0.7	1.0	215	205	335
	K-2	4.9	7.4	4.0	2.1	1.1	2.2	167	95	46	1.2	1.9	1.5	344	265	295
151	K-1	4.6	5.1	4.8	1.6	0.0	0.5	16	15	94	2.1	2.4	3.3	247	188	320
	K-2	4.5	6.0	4.3	1.7	0.7	0.5	131	12	69	0.7	1.3	1.0	202	244	201
160	K-2	4.9	8.5	6.9	0.4	2.6	1.2	61	350	80	1.1	2.1	1.6	356	203	124
166	K-1	4.5	4.7	4.9	1.1	1.1	1.3	135	12	5	1.3	0.6	2.1	244	187	205
	K-2	5.1	5.7	5.3	0.7	.09	1.1	83	20	5	0.6	0.9	1.1	216	270	257
175	K-3	3.9	6.0	5.2	0.8	1.7	1.2	67	175	27	1.6	1.1	2.2	198	136	151
179	K-1	5.1	4.5	4.3	1.9	2.0	2.4	14	35	105	1.7	1.5	1.8	282	270	362
	K-2	5.2	5.6	4.9	0.9	0.7	1.1	50	1	85	1.0	1.2	1.0	255	400	284
241	K-3	4.1	5.6	4.6	1.0	0.8	1.0	373	115	77	0.4	3.8	1.6	840	276	252
326	K-1	3.9	5.7	6.1	0.5	1.6	1.2	73	593	42	0.9	0.8	1.1	158	185	136
366	K-1	4.8	5.7	6.1	0.5	1.6	1.2	10	155	262	1.3	1.0	1.6	158	257	245
	K-2	5.1	7.4	5.5	1.0	1.2	2.1	205	162	255	1.2	1.0	1.5	179	234	240

tenuation of synthesis and translocation of enzymes involved in hydrolyzing polysaccharides and oligosaccharides. The rate of glucose transport diminishes, including that of glucose formed from hydrolysis of starch and maltose. Initially, glucose absorption increases, which could reflect an adaptive response to hypokinetic stress.[20,21]

Bed rest is generally associated with an initial increase in blood sugar, followed by a decrease, and then a subsequent increase during recovery.[7] Hypoglycemia is accompanied by higher levels of glucose-degradation products and greater activity of enzymes in blood and tissue, attesting to the activation of glucogenesis. Both lactate and the ratio of lactate to pyruvate increased. Increases in lactate indicate intentified glycolysis and glycogenolysis, i.e., an increase in carbohydrate utilization early in hypokinesia.

Blood sugar levels and the direction of carbohydrate metabolism are largely a function of the amount of glycogen in tissues. Restraining animals produces decreases in glycogen in the liver, skeletal muscles, and myocardium; these decreases were more substantial in all organs early in the treatment phase.[7,22] Exercising during bed rest, by contrast, increased tissue glycogen levels.[23] Glycogen in triceps biopsy samples was decreased by 39% after 5 weeks of bed rest; after 5 weeks of exercise, glycogen production was enhanced by 20%.[24]

Tissue glycogen levels reflect the balance between degradation and synthesis. Catabolism prevails in most cases, as demonstrated not only by diminishment of glycogen but also by accumulation of lactic acid, the product of its degradation. Glycogen stored in the liver is used to supply glucose to other tissues; however, these stores are depleted quickly, and thus other tissues can develop energy insufficiency once these stores are gone. This condition is manifested by hypoglycemia and high levels of free fatty acids in blood. Although tissue glycogen levels tend to recover during the later phases of hypokinesia, they usually do not return to baseline.

Restricting motion for humans probably reduces tissue glycogen as it does in animals. In addition to the direct evidence discussed above,[24] this conclusion is supported by indirect findings of decreases in blood sugar and increases in blood lactate. However, glycogen impoverishment of tissues in humans seems to be less severe than in animals. These changes probably represent an acute phase of adaptation, which lasts for different periods in humans vs animals. Carbohydrate metabolism is depressed for both groups under prolonged exposure. Aerobic conversion of carbohydrates is suppressed, as indicated by diminished oxygen consumption by tissues and a decreased ratio of phosphorus to oxygen (P/O_2), the latter being an indicator of the rate of oxidative phosphorylation.[25] The decreased P/O_2 ratio, and uncoupling of oxidation and phosphorylation, suggest that adenosine triphosphate (ATP) production may decrease in tissues during hypokinesia.

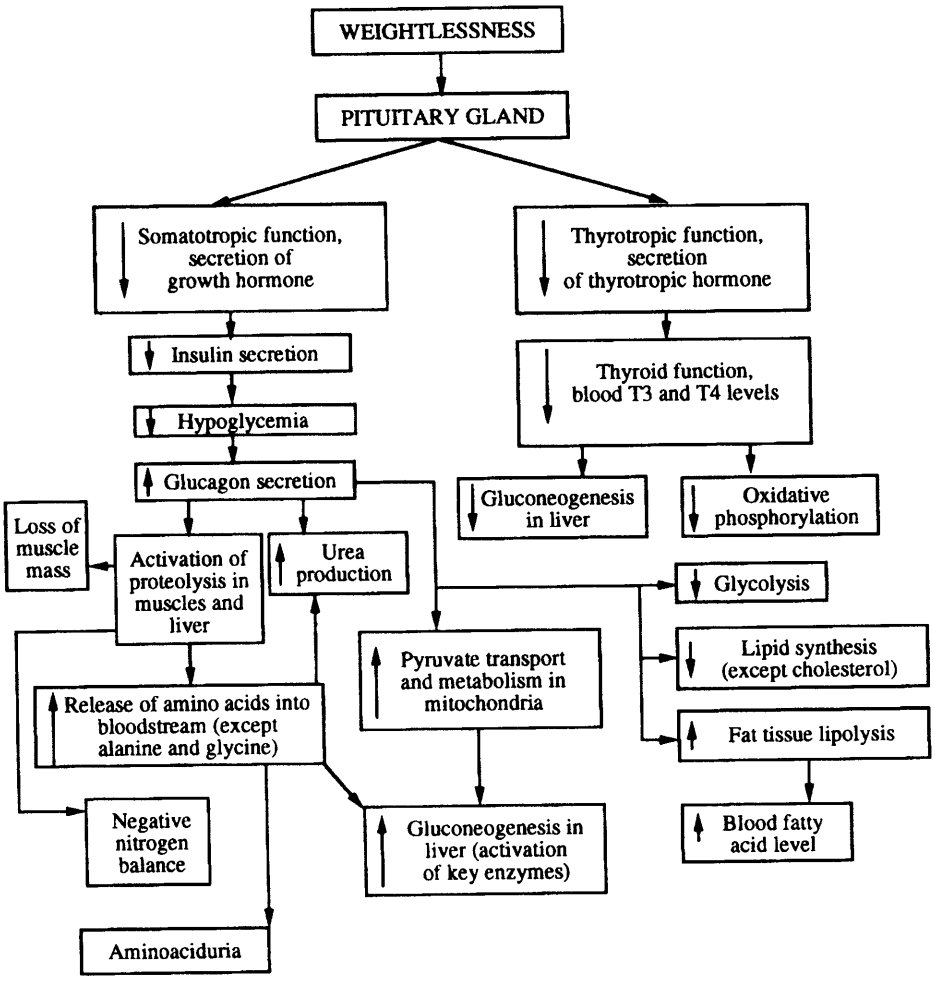

Fig. 1 Diagram of microgravity effects on metabolism.

Carbohydrate metabolism also depends on the endocrine function of the pancreas. Glycemic curves obtained during hypokinesia indicate that pancreatic function does not seem to adapt sufficiently to this state. These curves are used to assess glucose hydrolysis, transport, and assimilation. Pancreatic insufficiency of this type forces the body to use more fat to meet energy requirements. Many cosmonauts have shown signs of more intense carbohydrate metabolism on the first day after returning from long flights. These signs have included moderate hyperglycemia, accumulation of underoxidized products of carbohydrate metabolism (lactate and pyruvate), and increased insulin excretion. These measures usually return to normal in the ensuing 1 or 2 weeks.

Thus, carbohydrate metabolism in weightlessness and its simulations is marked by lack of significant changes in carbohydrate conversion in the gastrointestinal tract, hyperglycemia during early exposure, decreased insulin secretion and increasing hypoglycemia, inhibited aerobic carbohydrate oxidation, and accumulation of underoxidized products (lactate and pyruvate). Initial exposure seems to induce decreases in liver and skeletal-muscle glycogen and increases in glycolysis and glycogenolysis. Later, these processes return to normal, followed by inhibition. Decreases in the rate of aerobic carbohydrate conversion suggest uncoupling of oxidation and phosphorylation processes and diminished ATP production, which are responsible for energy production.

Exercise in actual or simulated weightlessness can modify carbohydrate metabolism, but not to any substantial degree. Greater energy requirements during the readaptation period probably facilitate the relatively rapid normalization of carbohydrate metabolism.

III. Lipid Metabolism

Lipids play crucial roles in anabolic and catabolic metabolism as well as being structural components of cells and their membranes. In one study, brief (2- to 14-day) exposure to the space environment led to increases in blood lipids. This increase, attributed mainly to triglycerides, probably reflects a stress-induced mobilization of metabolism during readaptation to Earth and impaired utilization of triglycerides in blood vessels. These subjects also had decreased plasma cholesterol, low-density lipoproteins, phospholipids (PL), and free fatty acids (FFA) on the first day after landing. Reductions in FFA

after landing may reflect their use as an oxidation substrate in skeletal muscles and the myocardium in weightlessness; the reduction in cholesterol could be associated with increased synthesis of mineralocorticoids.[26] A tendency toward lower blood cholesterol was observed in Apollo and Skylab crew members after flight.[4,27,28] In most cosmonauts who flew on Soyuz for five days or less, total blood cholesterol did not change significantly.[1] High-density lipoprotein fractions, considered a risk factor for cardiovascular disease, declined significantly in 125 Space Shuttle astronauts after flights lasting 2 to 10 days.[29,30] Total cholesterol, triglycerides, and low-density and very low-density lipoproteins in this group were no different from before flight.

Prolonged exposure to weightlessness sometimes leads to more active lipolysis and lipid utilization, manifested by decreased fat mass and increased plasma triglycerides and FFA (Table 2).[31] Lipid metabolism during readaptation to Earth was highly variable, and did not seem to be associated with flight duration.

Cell membrane structure and function can be modified by free-radical peroxidation; 2 to 5% of the membrane phospholipids are subject to this process. Intensified oxidation of polyene acyls in membrane phospholipids through a free-radical pathway leads to the formation of highly hydrophilic hydroperoxides, which alter membrane phase and permeability. An assessment of erythrocyte membranes from cosmonauts after a 150-day flight[31] revealed no evidence of lipid-peroxide accumulation. In fact, lipid peroxides were found to be below preflight baselines, which was attributed to decline in polyunsaturated fatty acids (linoleic acid) and the absence of arachidonic and eicosatrienic fatty acids. Higher levels of fatty acids in red blood cells, and enhanced lipid peroxidation, were found on the seventh day after landing. These findings can be considered adaptive and nonpathological, as confirmed by normal metabolism of red blood cells and normal permeability of their membranes to potassium ions. No signs of accumulated lipid peroxides or related impairment of red blood cells were detected in Skylab crew members.[4]

Products of lipid peroxidation (LPP) were elevated in blood samples from cosmonauts who had flown 150- and 211-day missions on the seventh day after landing. However, after flights of 240 days or more, elevated blood serum LPP levels were noted as early as the day after landing. Despite a general increase in total antioxidation activity and tocopherol concentrations, elevated LPPs persisted throughout the first week after landing. After a 1-year flight on Mir, crew members had differing amounts of diene conjugates, malonic dealdehyde, and Schiff bases, accompanied by increased total antioxidant activity. These measures all reverted to normal levels by the seventh day after landing.[32]

Rat experiments on Kosmos biosatellites have confirmed that weightlessness triggers lipid mobilization and lipolysis, reduction in subcutaneous adipose tissue and fat deposits, and accumulation of intermediate products of lipid metabolism in plasma, the liver, bone marrow, and other tissues. Morphological analysis of the livers of rats flown on biosatellites revealed fatty infiltration of the liver, with significant fat deposits distributed heterogeneously throughout the lobes, mainly in the vicinity of central veins, and in the sinusoids.[33] Both blood and tissue FFA levels in rats flown in space were higher than before flight[34–38]; both basal and hormone-stimulated triglyceride lipase activity were increased in white fatty tissue as well.[39] Reduced activity of 3-hydroxyacyl-CoA-dehydrogenase, which was found in the soleus and triceps of rats flown on Kosmos-1667,[40] inhibits oxidation of free fatty acids and increases their levels in blood.

Exposure to the space environment depresses the activity of the hepatic lipogenic enzymes, malate dehydrogenase, ATP-citrate-lyase, palmitate-CoA desaturase, diacylglycerol acyltransferase, and choline phosphoglyceride acetyltransferase.[41–45]

After flights on biosatellites, rats displayed decreases in total phospholipids in the sarcoplasmic reticulum and mitochondria of skeletal muscle,[46] and in the thymus and bone marrow, but not in the liver.[34,37] By the 26th day after landing, phospholipid levels had returned to normal; however, the microsomal fraction of skeletal muscles was found to contain lysophosphatidylcholine, a polar phospholipid, which can disrupt the arrangement of fatty acid residues in membranes and activate lipid peroxidation.

Liver, thymus, bone marrow,[34–37] and muscle[47] tissues of rats flown in space had higher triglyceride levels than before flight. As a rule, total hepatic cholesterol was unchanged, but was frequently elevated in blood plasma.[34–38]

Lipid metabolism has been studied extensively in simulations of weightlessness with humans and animals. During a 120-day head-down bed-rest study, an increase in cholesterol esters that raised total cholesterol level was noted starting on the 72nd day, with a tendency toward decreases in phospholipids and total FFA. Triglyceride levels increased significantly on the 28th and 72nd days of bed rest. With respect to the fatty acid spectrum, saturated acids consistently dominated unsaturated, and linolenic acid was in deficit.[48] Analogous trends have been noted for longer bed-rest periods (up to 370 days).[49,50] Levels of triglycerides, cholesterol and its free fraction, and the atherogenic ratio of low- to high-density lipoproteins all were elevated; levels of phospholipids and their transport forms and high-density lipoproteins were reduced. Such changes reflect a disruption in the balance between hydrolysis and assimilation of lipids in the gastrointestinal tract, and characteristics of lipid transport and metabolism in organs and tissues.[21] Shifts in lipid metabolism were the most extreme, both for humans and animals, when countermeasures were not used during hypokinesia.

Exposure to actual or simulated weightlessness causes changes in lipid metabolism that take the form of intensified lipolysis and mobilization of lipids; increases in plasma levels of total lipids, triglycerides, FFAs, and cholesterol; and activation of lipid peroxidation. Such changes are adaptive, are governed by the neuroendocrine regulatory system, and probably reflect reliance on lipids for anabolic and catabolic metabolism during exposure to spaceflight or other "extreme" conditions.

IV. Enzyme Activity

A. Protein Metabolism

Enzyme activity in blood and tissues reflects metabolic processes in the body, and is important in understanding both individual biochemical reactions and metabolism as a whole. Transaminase activity is an excellent indicator of protein metabolism, as transaminases promote deamination of amino acids and formation of new nonessential amino acids from carbohydrates and the products of lipolysis. No significant changes were noted in cosmonaut serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT)[4,51] after missions lasting 30 to 185 days. However, after shorter missions (up to 60 days), blood serum AST activity was increased.[52] Prolonged horizontal bed rest did not affect serum transaminases, but head-down bed rest did: ALT activity did not change early during bed rest, but increased later, and AST activity increased early.[53] AST activity was increased during a 370-day head-down bed-rest study as well, peaking during months 4–6, and then declining during months 10–12. ALT activity significantly exceeded baseline in months 4 and 12. AST activity was affected by the use of countermeasures early or late in the bed-rest period, whereas that of ALT was not. Activity of both enzymes was elevated during the first week of recovery.[53]

Rats undergoing hypokinesia showed diminished ALT activity during the first day of treatment followed by a stable increase; AST activity did not change on the first day, but increased later.[54] The activity of both enzymes increased with the duration of hypokinesia, peaking at the end of the hypokinesia period (30 or 60 days). The supposition that increased serum transaminase activity was linked to its release from tissues[55] was confirmed by high activity of both enzymes in soleus biopsy samples from humans after prolonged head-down bed rest. Transferase activity in venous blood after 5 days of bed rest was much higher than baseline. Relative activity in different organs varied, being elevated in venous blood from the brain, liver, kidneys, and arm and leg muscles, but almost unchanged in arterial blood.[56]

The activity of cathepsins (tissue proteolytic enzymes) increased progressively in rats undergoing hypokinesia, and total tissue amino acid levels diminished.[57] The rate of proteolysis did not decrease in rats during the first weeks of hypokinesia, nor were there changes in the pool of free amino acids. Later in the treatment, an increase in proteolysis rate was accompanied by a simultaneous decline in total free amino acids, which probably were used in gluconeogenesis. These changes in aminotransferase and tissue cathepsin activities attest to the predominance of catabolic protein metabolism in animal and human tissue during hypokinesia.

B. Carbohydrate Metabolism

After long-term flights, cosmonauts usually show significant changes in the activity of enzymes of carbohydrate metabolism. The activity of blood serum lactate dehydrogenase (LDH) decreased, as did that of the Krebs cycle enzymes malate dehydrogenase (MDH) and isocitrate dehydrogenase (ICDH). Neither MDH nor ICDH are involved in oxidative reactions; MDH activity often dips below the normal range with characteristic isoenzyme redistribution in blood serum, i.e., increases in the cytoplasmic form and decreases in the mitochondrial form of this enzyme. Creatine phosphokinase (CPK) activity, an enzyme of anabolic homeostasis, in serum increased after both short-term and long-term flights.[51,52]

Serum enzyme activity was variable after a 370-day head-down bed-rest period.[53] LDH activity increased until day 110 and declined gradually thereafter, and recovered slowly. This pattern was not affected by the use of countermeasures. Shifts in LDH activity were a function of changes in isoenzymes specific to aerobic energy metabolism. Subjects who exercised regularly had only slight changes in MDH activity, with an increase noted on bed-rest day 50. Activity of glutamate dehydrogenase decreased in all subjects late in the bed-rest period. ICDH activity decreased gradually, with no appreciable differences in subjects who began countermeasures early or late in the bed-rest period. CPK activity declined gradually during the bed-rest period regardless of countermeasures. Changes in total CPK activity were predominantly due to isoenzyme activity in skeletal muscle. During the recovery period, both muscle and myocardial CPK activities increased sharply.

The amounts of enzymes involved in energy metabolism in animals seem to change at different rates in different organs as a function of the duration of restricted movement. Serum LDH activity increased; skeletal-muscle LDH activity increased early during hypokinesia, and then decreased progressively. LDH activity varied among different muscles and was correlated with lactate levels. The direction of change in LDH activity and lactate levels during hypokinesia were the same in the myocardium and liver.[58]

Aldolase, another important enzyme involved in anaerobic conversion of carbohydrates, also was studied during hypokinesia. Horizontal bed rest and water immersion were not associated with changes in aldolase activity, but it dropped sharply toward the end of a head-down bed-rest period.[59,60] Aldolase activity increased in the blood serum and myocardium but decreased in the skeletal muscles of restrained rats.[61,62] The activity of α-glycerol-phosphate dehydrogenase (α-GPDH), an oxidative enzyme of anaerobic carbohydrate conversion, was elevated in soleus biopsy samples from humans undergoing prolonged head-down bed rest.[55] Activity of α-GPDH also was increased in lymphocytes of rats restrained for up to 20 weeks.

Increases in the activities of LDH, aldolase, and α-GPDH, all of which participate in anaerobic metabolism of carbohydrates, during the early period of hypokinesia, with increases in the amount of lactic acid, imply an intensification of the glycolytic process. However, these changes were reversed later in the hypokinetic period, which underscores the importance of considering individual

differences, experimental conditions, and other factors in interpreting effects of this kind.

C. Energy Metabolism

The condition of an organism exposed to simulated or actual weightlessness is determined by the quantity, quality, and distribution of high-energy metabolites and the body's ability to produce them and use their energy. CPK activity in human blood serum decreased consistently during prolonged bed rest, but it increased in rat blood on the 15th and 22nd days of restricted movement, and increased in the myocardium.[62] CPK activity in the soleus, anterior tibia, and gastrocnemius muscles increased several-fold, but was no different from baseline in other muscle groups.

Among the enzymes involved in hydrolyzing high-energy bonds, only the activity of adenosine triphosphatase (ATPase) was studied in hypokinesia. Gastrocnemius microfibers collected from humans before and after a 49-day head-down bed rest showed decreases in ATPase activity.[63] ATPase activity in organs and tissues of restricted rats was diminished.[7] The activity of calcium-activated ATPase in the myocardium and kidneys rose, but that of magnesium-activated enzyme was unchanged. This reduction in ATPase activity could be a response to diminished motor activity. The increase in CPK activity in skeletal muscles and blood suggests intensified transport of phosphate from creatine phosphate to adenosine diphosphate (ADP) and possibly of the reverse reaction, i.e., formation of creatine phosphate through ATP creatine phosphorylation.

Alkaline and acid phosphatase activities also were evaluated in animals and in humans after spaceflights. Alkaline phosphatase is involved in phosphorus and calcium metabolism in bone. Elevation of acid phosphatase, a lysosomal enzyme, indicates that lysosomes are being destroyed and their enzymes released.

Blood serum alkaline-phosphatase activity increased during the second through fourth weeks of recovery after long missions. Its isoenzyme spectrum indicated uniform activation of both liver and bone isometric forms of this enzyme.[51] Alkaline phosphatase activity increased toward the end of a 120-day head-down bed-rest study, perhaps because of activation of its bone isoenzyme.[64] After the bed rest was terminated, bone alkaline phosphatase activity decreased sharply, but that of the liver increased regardless of whether countermeasures were used or not. Activation of this enzyme was not uniform throughout the body; early during bed rest, no changes in alkaline phosphatase activity were seen in blood flowing from the brain and liver, but activity in blood from the myocardium, kidneys, and muscles of lower extremities had increased significantly.[43,56]

Previously we described changes in oxidizing enzymes of the Krebs cycle (MDH and ICDH) and their isoenzymes after space missions of different durations. Analogous changes were noted during simulations of weightlessness (bed rest, water immersion), in which enzyme activity declined after a few days of exposure. This decrease probably results from unloading of the musculoskeletal system, and thus can be associated with energy utilization and production by the body in weightlessness. Skeletal muscles, myocardium, and liver of restrained rats all showed decreases in NAD-dependent enzyme activity (including ICDH). The activity of α-ketoglutarate dehydrogenase increased in the soleus and tended to decrease in liver tissue. Succinate dehydrogenase activity was suppressed in skeletal muscle, myocardium, brain, and lymphocytes of restrained rats and in human lymphocytes after spaceflight and laboratory simulations.[65–70]

Other oxidizing enzymes not involved in the Krebs cycle, i.e., pyruvate dehydrogenase, β-oxybutyrate dehydrogenase, and glutamate dehydrogenase, tended to show reduced activity at various points during hypokinesia.[7] Finally, the activity of cytochrome oxidase, the terminal enzyme of the biologic oxidation chain that enters into immediate contact with oxygen, decreased for the most part in skeletal muscles, brain tissue, liver, kidneys, and lungs of rats exposed to prolonged hypokinesia.

V. Vitamin Metabolism

Vitamins are essential nutrients. Most vitamins are active components of enzymes and are necessary for metabolic processes under varying physiological conditions. Vitamins play an important part in adaptation to extreme environments, including that of spaceflight.

Body levels of several water-soluble vitamins (thiamine, riboflavin, niacin, and pyridoxine) in crew members were assessed after long spaceflights. Concentrations of parent compounds and metabolites were measured in urine samples, and the activity of vitamin-dependent enzymes was measured in red blood cells as well.[70,71] The crew members studied consumed a standard diet before and after flight. Despite strenuous exercise, preflight vitamin levels generally met standard recommendations, probably because the crew members used multivitamin supplements.

On the first day after landing, daily renal excretion of thiamine and pyridoxic acid had diminished substantially, and riboflavin and N1-methylnicotinamide excretion may have decreased as well. By the seventh day after landing, renal excretion of vitamins and their metabolites had increased, except for N1-methylnicotinamide, but still remained below preflight levels. Postflight activity of transketolase in red blood cells increased, but thiamine diphosphonate activity remained at baseline level. Glutathione reductase activity in red blood cells had decreased immediately after flight, but had increased by one week thereafter. The effect of flavin adenine dinucleotide (FAD) tended to increase. The activation coefficient of AST in red blood cells indicated that body supplies of pyridoxine were adequate; however, this measure had increased by the seventh day after landing. Total blood NAD and NADP did not change from baseline values.

Serum concentrations of folic acid and cyanocobalamin were both elevated immediately after a 211-day mission; the

former was still high on the seventh day after landing, but cyanocobalamin had subsided to preflight values by that time. These two factors play important roles in hemopoiesis, which also seems to change as a result of spaceflight.

Head-down bed rest lasting up to 12 months markedly suppressed the renal excretion of thiamine throughout the treatment period; the most extreme suppression took place in the the group that exercised throughout the bed-rest period. Analogous changes were noted for 4-pyridoxic acid excretion. Transketolase and AST activity in red blood cells was increased at all measurement points; on the seventh day after treatment, the activity of vitamin-dependent enzymes in red blood cells was reduced. The AST activation coefficient was virtually unchanged in all subjects regardless of whether countermeasures were used, indicating that pyridoxine was adequate.

Vitamin B_{12} and folic acid also were examined during the year-long bed-rest study. On day 100, folic acid in blood serum and red blood cells had increased in both groups of subjects. Serum cobalamin was elevated on day 170. For the remainder of the experiment, serum and red blood cell concentrations of folic acid were elevated in both groups, to a greater extent for the "regular countermeasures" group. Subjects given folicobalamin toward the end of the bed-rest period produced the highest increase in folic acid levels in blood serum and red blood cells, considerably exceeding the upper limit of normal. Changes in blood serum vitamin B_{12} concentration were less extreme. In subjects who did not exercise during the initial portion of head-down bed rest, serum cobalamin level was above baseline, and peaked after folicobalamin administration. Subjects who exercised throughout the treatment period had serum cobalamin concentrations only slightly greater than baseline values. Serum cobalamin was decreased on the seventh day of recovery, but increased on the 60th day. Folic acid in red blood cells were elevated on days 30 and 60 of recovery.

These assessments of vitamin metabolism after spaceflight suggest that prolonged exposure to weightlessness markedly affects the metabolism of water-soluble vitamins such as thiamine, riboflavin, pyridoxine, and niacin, as well as the vitamins involved in hemopoietic processes. Prolonged head-down bed rest generally was associated with similar changes in vitamin metabolism. Countermeasures (exercise and drugs) used during flight or its simulations seem to provoke shifts in thiamine and pyridoxine levels earlier in the exposure.

VI. Blood Cell Metabolism

Numerous abnormalities have been noted in hematological indicators after exposing humans to spaceflight conditions. Hemoglobin, reticulocyte, and red blood cell mass and counts are typically depressed after long flights, and red cell shape, size, and metabolism are changed as well.[72,73] Reticulocyte counts and erythropoietin production are activated during the postflight recovery period. Changes in white blood cell counts and composition have been less stable, with leukocyte counts and ratios returning to baseline within 24 hours after landing.

Spaceflight factors do not seem to cause pathological shifts in the structure or function of blood cells. Some deviations have been noted in the activity of cytoplasmic granules of white blood cells with segmented nuclei after long missions, as well as increased polysaccharides in lymphocyte cytoplasm.

Electrophoretic mobility of red blood cells reverts to normal soon after flight, with the charge distribution becoming normal by 2 to 3 weeks after landing. Electrophoretic separation of red blood cells revealed an association between the normalization of mean red blood count and charge-distribution curves.

An increase in the number of red blood cells with high hemoglobin levels on the day of landing could be considered a compensatory response. Red blood cells in specimens obtained in space showed crenation,[73] which was not present after flight. Cytological analyses and electron microscopy performed after long missions revealed no significant change in red blood cell membranes.

The causes of decreases in red blood cell mass, hemoglobin, and osmotic resistance are still unknown. The reduction in red blood cell mass is probably caused by a decrease in the rate of erythropoiesis; however, some other mechanism leading to hemolysis of a portion of red blood cells is suggested by data indicating a threefold increase in red blood cell hemolysis rate in rats flown on Kosmos-782 and Kosmos-936.[74] In-flight biochemical studies of red cells aboard Skylab did not reveal any hemolytic changes; however, changes were noted in intermediate products of glycolysis and in enzyme activity.[4] Oddly shaped red cells, particularly echinocytes, persisted for some for two or three months of flight, but disappeared within 2 or 3 hours of landing. The changes in shape did not impair provision of adequate blood and oxygen to tissues.

Consistent changes in red cell metabolism have been found after long flights, and have generally taken the form of shifts in energy generation (glycolysis) and decreases in ATP and the reduced form of glutathione (GSH).[75] As a rule, these decreases were accompanied by an increase in glucose-6-phosphate dehydrogenase and some enzymes of the antioxidant system, probably as a compensatory response serving to increase the level of reduced glutathione and maintain the structural integrity of the cell. The diminished amount of reduced glutathione after long missions was attributed to an increase in its oxidized form as well as a decrease in synthesis of the tripeptide, as indicated by data on accumulation of free amino acids in blood plasma.

Deviations in red blood cell metabolism related to weightlessness probably are not due to impairments within the cell, but rather may reflect the development of compensatory responses serving to prevent disruption of the membrane. This idea is supported by studies of ATP levels and special analyses of the physicochemical properties of the membrane conducted after 150-, 160-, 326-, and 366-day spaceflights and prolonged head-down bed rest. Decreases in energy-metabolic rate observed after 160- and 326-day missions were associated with changes in the lipids and phospholipid spectra of membranes, as indicated by greater amounts of free cho-

lesterol, esters, and decreased phospholipids. Thus, the cholesterol-phospholipid ratio increased, and the membrane microviscosity and rigidity as well, the latter verified by shifts in the ratios among phospholipid fractions and a significant decrease in phosphatidylethanolamine (PEA) concentrations. Changes in PEA may have resulted from increased uptake of this fraction in phosphatidylcholine synthesis, as well as from increased utilization by cellular membranes. Higher rates of PEA utilization optimize processes such as phospholipase and insulin activation, detoxification, and stabilization of lipoprotein and energy metabolism.

Shifts in membrane lipids foster changes in protein-lipid interactions and membrane functions, as indicated by diminished activity of Na^+,K^+-dependent ATPase, higher cellular resistance to acid hemolysis, and resistance to cell deformation, all found after 326-day and 366-day spaceflights. After the 326-day flight, Na^+,K^+-dependent ATPase activity decreased and Ca^{++}-ATPase increased, probably representing a compensatory mechanism to eliminate excessive calcium, which makes the cellular membrane more rigid and alters its shape. After the 366-day mission, increases in resistance of red cells to acid hemolysis, deformation, and activity of Na^+,K^+-dependent ATPase were accompanied by some reduction in Ca^{++}-dependent ATPase. One cosmonaut showed elevated cell-metabolic activity at 1, 6, and 70 days after landing; the other had decreases in ATP, in reduced glutathione, and in glucose-6-phosphate dehydrogenase activity. These indicators had not returned to normal by the 70th day after landing.

Structural and conformational changes in erythrocyte membranes have been found during a 370-day head-down bed-rest period; these changes took the form of deviations in lipid composition, activity of membrane-bound enzymes, sensitivity of beta-adrenoreceptors, and binding of a fluorescent probe with the membrane.[76] Changes were the most extreme on days 50, 110, and 350 of bed rest and on the first and seventh days thereafter. These changes could have resulted from concurrent increases in free cholesterol and atherogenic ratio, as well as decreases in calcium and epinephrine concentrations.

These changes are similar to those observed after long spaceflights, specifically, decreases in absolute levels of phospholipid fractions containing saturated fatty acids, and increases in the proportion of polyunsaturated arachidonic acid, in red cell membranes. These changes suggest that the membrane structure is modified through replacement of saturated acids with unsaturated acids. However, absolute level of arachidonic acid was no different before vs after flight. Changes in phospholipid composition could explain the decrease in membrane elasticity, perhaps by altering the number of double bonds in fatty acid molecules. Changing the elasticity of a membrane affects the function of that membrane, including enzyme catalysis, ion transport, and synaptic transmission. Replacing an 18-carbon chain with a 20-carbon chain can affect membrane size, improve resistance to deformation, and eventually reduce the ability of red blood cells to transport hemoglobin. For this reason, the results of electron microscopy showing changes in shape of red cells in cosmonauts are of considerable interest.

Long space missions and head-down bed rest also have been associated with the presence of eicosanoids (unusual long-chain polyunsaturated fatty acids) in blood serum and red blood cell membranes. Eicosanoids are precursors of prostaglandins (PG). Prostaglandin-synthetase activity, which reflects the ability of tissue to transform arachidonic acid into PG, begins to produce abnormal products in the cells with unusual membrane composition. Replacement of even one cis-double bond with a trans-bond in the triene fragment of a C-20 polyunsaturated fatty acid, or shifting the double bond by a single place, can transform it from a substrate for PG biosynthesis to an inhibitor.

Thus, the presence of eicosanoids in blood serum and red blood cell membranes after long missions and ground simulations suggests the possibility of PG destruction and suppression of PG synthesis by eicosanoids on the one hand, and possible generation of eicosanoids through transformation of specific cell structures in the central nervous system, cardiac muscle, kidneys, and liver on the other. Lipid metabolism in serum and red blood cell membranes in rats undergoing tail suspension (60 days) and humans exposed to hypokinesia (370 days) showed increases in serum and red-cell membrane amounts of free fatty acids that can act as surfactants. The formation and extraction of protein-lipid complexes from the cell membrane (through replacing membrane components with detergents) can eventually destroy the cell membrane. The composition of the free fatty acid fraction differed from that of phospholipid fraction because of the presence of two stereoisomers, isopalmitic and isostearin acids. Information about the presence of branched fatty acids such as these in animals is scanty, and their function in the human body is not clear. The presence of such unusual isomers in blood merits further study.

To summarize, the structural and functional changes in biological membranes present after spaceflight or its simulations verify that lipid metabolism is affected at the cellular level. Changes such as these might be expected to affect ion transport, synthesis of PG, and the activity of membrane-bound enzymes on long spaceflights.

VII. Summary and Conclusions

Many environmental factors, both normal and extreme, affect living things by influencing their metabolism. Biochemical responses to weightlessness are the body's attempt to create a new level of physiological homeostasis appropriate to the new environment.

One chief effect of gravity, weight loading, is crucial for locomotion and physical activity on Earth. The constant flow of impulses from the "loaded" musculoskeletal system helps to regulate the direction and rate of metabolic processes. In weightlessness, the abrupt transition from normal motor ac-

tivity to hypodynamia (and relative hypokinesia) is a stress factor of proportional intensity to the abruptness of the transition.

Protein degradation prevails over protein synthesis during hypodynamic/hypokinetic conditions, as indicated by decreases in total body mass and its organs and tissues; negative nitrogen balance; slowed protein synthesis (as indexed by excretion of heavy nitrogen administered in glycine); increased renal excretion of total nitrogen, urea, uric acid, creatine, creatinine, sulfur, and amino acids; and increased activity of tissue proteolytic enzymes and aminotransferases. Prevalence of catabolic processes results from higher rates of catabolism and from depression of anabolic processes. Attempts to bolster protein synthesis by supplying space crews with additional amino acids have not met with success; nor has the use of specially balanced protein/amino acid diets during hypokinesia (bed rest), or giving restrained animals high-protein food in combination with anabolic drugs.

Energy production is thought to be enhanced during the acute phase of adaptation through use of the glycogen from the skeletal muscles and the liver. The rates of glycogen synthesis and utilization slow later in adaptation; the main pathway of formation of high-energy phosphate bonds—oxidative phosphorylation—is blocked and anaerobic conversion of carbohydrates takes over. One likely mechanism underlying the uncoupling of phosphorylation and oxidation is hormonal activation of lipolysis and accumulation of FFAs, which are powerful natural metabolites. Accumulation of FFAs suggests that fats are the primary source of energy in spaceflight. As a result, $NADH_2$ in the respiratory system is replaced by $FADH_2$—the product of oxidation of fatty acids at their first stage of β-oxidation. When $FADH_2$ is oxidized in the respiratory system, one of the conjugation bonds is lost, and thus oxidative phosphorylation produces two ATP molecules instead of three. High amounts of calcium in blood and tissues also could cause uncoupling of the oxidation and phosphorylation processes.

The major substance inducing oxidative phosphorylation is ADP, a by-product of natural ATP utilization. If ATP utilization is reduced because of limited motor activity, ADP production and oxidative phosphorylation diminish. Diminished phosphorylation in the respiratory system, normally the main source of energy, seems to be compensated for by increased glycolysis. However, activation of glycolysis is a temporary solution at best. Disruption of energy production also can play roles in impaired crew performance, fatigue, and chronic weakness, all of which can arise from prolonged exposure to weightlessness and its simulations.

Changes in lipid metabolism after brief missions probably result from acute adaptation/readaptation stress, and may be regulated hormonally. Lipid metabolism after long missions or ground-based simulations is characterized by high concentrations of cholesterol, triglycerides, low-density and very low-density lipoproteins, elevated ratios of low-density to high-density lipoproteins, decreased ratios of phospholipids to cholesterol, and increased amounts of unsaturated fatty acids. These atherogenic effects can interfere with several physiological functions, including the immune properties of blood, the structure of endothelial vessels, and the structure and function of cell membranes. At later stages of exposure to actual or simulated weightlessness, tissue proteins are lysed and the products converted to fat. Most of the free fatty acids released during lipolysis also are converted to fat.

Products of lipid peroxidation probably also contribute to the metabolic changes noted in weightlessness and restricted motion. Intensified lipid peroxidation is a nonspecific response to extreme situations. Peroxides suppress nucleic acid synthesis, impair cell division, and damage chromosomes, mitochondrial membranes, and lysosomes. Products of lipid peroxidation inhibit many cytolytic enzymes. Lipid peroxidation is apparently increased under conditions of hypokinesia, with the rate being a function of subject age and the efficacy and adequacy of countermeasures. Recovery after hypokinesia is characterized by adaptive stress, manifested as a sharp increase in lipid peroxidation. Activation of this process in biological membranes could well underlie some aspects of cell pathology.

Studying the enzymes associated with energy metabolism helps clarify how carbohydrate metabolism is modified in weightlessness. Changes in the activity of the glycolytic enzyme LDH and enzymes of the tricarboxylic-acid cycle (MDH, ICDH and their isometric forms) attest to changes in energy metabolism under these conditions. Glycolysis is activated during the acute phase of adaptation, and aerobic and anaerobic oxidation are inhibited during prolonged exposure to weightlessness. These changes not only attest to the diminished intensity of the main energy-producing processes, but also reveal changes in the permeability of membrane structures at the cellular and subcellular levels.

In summary, prolonged exposure to space is accompanied by intensified catabolic processes and a gradual decline of many metabolic reactions, especially those responsible for energy production. Metabolic changes in response to long-term spaceflight, as well as during prolonged hypokinesia, are adaptive. Of concern from the standpoint of future pathology are changes in protein, lipid, carbohydrate and energy metabolism that may be associated with pituitary insufficiency. These changes include a decrease in the pool of total and essential amino acids and α-globulins, accompanied by a considerable increase in β-globulins and retardation of the process of biological synthesis. Impairment of the balance between lipid peroxidation and antioxidant protection could give rise to prepathological metabolic and structural changes.

Assessing an individual's metabolic state under continuous exposure to several factors (e.g., countermeasures such as exercise, lower body negative pressure, or drugs; weightlessness; and the artificial habitat) is a difficult undertaking. The use of computer-generated models of the weightless environment thus is indispensable in order to fill the gaps in research that has been conducted on spaceflights. Synthesis and extrapolation of data from space missions and ground simulations and animal experiments can greatly facilitate our under-

standing of the biochemical responses of humans as they adapt to the unique spaceflight environment—and again as they readapt to more familiar conditions on Earth.

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